Amendments to the Specification:

Please replace the paragraph bridging pages 8 and 9, with the following amended paragraph:

To date, a variety of methodologies have been employed to stabilize engineered antibodies. First, introduction of additional di-sulfide bonds has been performed through molecular biological manipulation of the antibody-expressing construct (Reiter Y. and Pastan I. TIBTECH; vol. 16(12): pp. 513-520, 1998). Second, introduction of a linker has been employed that allows both fragments to be expressed as a single chain (single chain Fv fragments) (Pluckthun and P. Pack. Immunotechnology; vol. 3(2): pp. 83-105, 1997; Cao Y. and Suresh M. R. Bioconjugate Chemistry; vol. 9(6): pp. 635-644, 1998). Finally, fusion of an exogenous di- or oligomerization domain to each of the Fv fragment chains has been performed (Pluckthun and P. Pack. Immunotechnology; vol. 3(2): pp. 83-105, 1997; Cao Y. and Suresh M. R. Bioconjugate Chemistry; vol. 9(6): pp. 635-644, 1998; see also Antibody Engineering Page, IMT, University of Marburg, ~~FRG: http://aximt1.imt.uni-marburg.de/_rek/indexfenster.html)~~ FRG.

Please replace the paragraph at page 37, lines 21-33, with the following amended paragraph:

The most direct way of accumulating sequences is by cloning and sequencing cDNAs of proteins that contain the domains/modules of interest. Sequence data is becoming more and more available through the efforts of the genome projects. Much of the sequence data is available in databases that can be accessed through the internet, or otherwise, and furthermore there are several published sources that have accumulated sequences of specific domains/modules. One such collection of specific sequence data is the Kabat Database of Sequences of Proteins of Immunological Interest (~~http://immuno.bme.nwu.edu;~~ Johnson, G. et al. Weir's Handbook of Experimental Immunology I. Immunochemistry and Molecular Immunology, Fifth Edition, Ed. L. A. Herzenberg, W. M. Weir, and C. Blackwell, Blackwell Science Inc., Cambridge, Me., Chapter 6.1-6.21, 1996) that contains, among other things,

sequences of immunoglobulin molecules (see Sections 6-8, Examples). Such sequence data is also available from ~~Genebank~~ Genbank® ~~(http://www.ncbi.nlm.nih.gov)~~.

Please replace the paragraph at page 38, lines 3-7, with the following amended paragraph:

The first approach is to mine databases of existing structural co-ordinates for the proteins of interest. The data of solved structures is often available on databases that are easily accessed in the form of three-dimensional coordinates (x, y, and z) in Angström (10^{-10} m) units. Often this data is also accessible through the internet (*e.g.*, on-line protein structure database of the National Brookhaven ~~Laboratory: www.nbl.pdb.gov~~ Laboratory).

Please replace the paragraph at page 57, lines 24-31, with the following amended paragraph:

The polypeptides now containing tyrosyl side-chains at the residues to which the cross-link reaction should be directed are subjected to the cross-link reaction under the conditions determined as described above and carried out, also as described above. The efficiency of the reaction may be examined, for example, by Western blotting experiments, in which a cross-linked complex should run at approximately the molecular weight of both or all polypeptides of the complex. If the bond is readily formed under the above conditions, the strength of the reaction ~~my~~ may still be further adjusted to the minimally required strength.

Please replace the paragraph bridging pages 61 and 62, with the following amended paragraph:

Utility of a stabilized polypeptide or complex can be determined directly by measuring its pharmacological activity, either in ~~animial~~ animal studies or clinically. In a specific embodiment, such measurements may include, for example, measurements with which tumor ~~pro-~~ progression or regression is monitored upon treatment of an animal model or one or several patients with a stabilized polypeptide or complex designed as an anti-cancer

pharmacological agent. In another embodiment, such measurements may include, for example, ~~measurements, of~~ measurements of bone mass, such as x-ray measurements, upon treatment of an animal model or one or several patients with a stabilized polypeptide or complex designed as an anti-menopausal bone-loss pharmacological agent.

Please replace the paragraph bridging pages 69 and 70, with the following amended paragraph:

The target must be in an environment that is accessible to immunoglobulin-derived products, such as, for example, serum, the extracellular ~~matix~~ matrix, the brain, or the intracellular space by way of liposomes (Hoffman R. M. J. Drug Target.; vol. 5(2): pp. 67-74, 1998) or peptide induced cellular uptake (Schwarze S. R. et al. Science; vol. 285: pp. 1565-72, 1999). For intracellular applications of immunoglobulin, see Bosilevac J. M. et al. J. Biol. Chem.; vol. 273(27): pp. 16874-79, 1998; Graus-Porta D. et al. Mol. Cell Biol.; vol 15: pp. 1182-91, 1995; Richardson J. H. et al. Proc. Nat. Acad. Sci., USA; vol. 92: pp. 3137-41, 1995; Maciejewski J. P. et al. Nat. Med.; vol. 1: pp. 667-73, 1995; Marasco W. A. et al. Proc. Nat. Acad. Sci., USA; vol. 90: pp. 7889-93, 1993; Levy Mintz P. et al. J. Virol.; vol. 70: pp. 8821-32, 1996; Duan L. et al. Hum. Gene Ther.; vol. 6(12): pp. 1561-73, 1995; and Kim S. H. et al. Mol. Immunol.; vol. 34(12-13): pp. 891-906, 1997. A favorable environment is present in all tissues and organs that are reached by the blood supply, and where the target molecule is present on the cell surface or in the extra-cellular matrix. Since the functionality of immunoglobulin-derived Fv fragments is primarily to bind to target molecules, binding to the target should preferably suffice to accomplish the desired therapeutic or diagnostic effect. Catalytic functionality is, however, also known for immunoglobulin, and may therefore also be achieved in pharmacological and/or industrial contexts (Pluckthun A. et al. Ciba Found. Symp.; vol. 159: pp. 103-12; discussion 112-7, 1991; Kim S. H. et al. Mol. Immunol, vol. 34: pp. 891-906, 1997).

Please replace the paragraph at page 71, lines 8-30, with the following amended paragraph:

Residue amino acid usage data is data compiled on amino acids encoded and expressed at each residue of known and sequenced Fv fragments. It is collected in, and obtained from, the publication "Proteins of Immunological Interest", Kabat and Wu, Government Printing Office, NIH Publication 91-3242, 1991 ("K&W"). The amino acid sequences in this publication are ordered according to a standardized numbering system that takes into account the gene structure of the heavy and light chain variable regions. In the variable regions of the heavy and light chains alike, four Framework Region segments (FRs)--which are relatively conserved--are interspersed by three--highly variable--Complementarity Determining Regions (CDRs). The CDRs contain the amino acids that determine the antibody's specificity, and that physically contact the antigen. Aligning all sequences according to the K&W numbering system was very important for the purpose of performing a statistical analysis as described in this example since the corresponding residues of the FRs are thereby always aligned, regardless of the varying sequence lengths of the interspersed CDRs. This ensured that statistical measurements were made with sets of data containing appropriate and comparable data points. Coordinate data for distance calculations of all atoms other than hydrogens of 17 Fv fragments from crystallographically solved immunoglobulin structures was downloaded from the protein structure database Brookhaven National Laboratory (~~www.bnl.pdb.gov;~~ FIG. 5). These data provide the three-dimensional coordinates (x, y, and z) for each atom in a solved structure, expressed in metric units, i.e. Angströms (~~10-10 m~~ 10^{-10}m, Å). With this data it was possible to calculate the three-dimensional distances between any desired atoms (*e.g.*, amino alpha and beta carbon atoms) and to calculate statistical measurements of the variability of such distance between the different Fv fragments in the sample being analyzed (FIGS. 5, 6, and 7).

Please replace the paragraph at page 108, lines 12-18, with the following amended paragraph:

Coordinate data for distance calculations of all atoms other than hydrogens of CALB was downloaded from the protein structure database Brookhaven National Laboratory (~~www.bnl.pdb.gov;~~ FIG. 5). These data provide the three-dimensional coordinates (x, y, and z) for each atom in the solved structure, expressed in metric units, i.e. Angströms (10^{-10}m, Å). These data also contains the amino acid sequence of the polypeptide. With this data it was possible to calculate the three-dimensional distances between any desired atoms (*e.g.*, alpha and beta carbon atoms).

Please replace the paragraph bridging pages 118 and 119, with the following amended paragraph:

Coordinate data for distance calculations of 3 related subtilisin proteins (subtilisin E and BPN, and subtilisin from *Bacillus lentus*) from crystallographically solved structures was downloaded from the protein structure database at Brookhaven National Laboratory ~~(http://www.pdb.bnl.gov or http://www.rcsb.org; files1SCJ, 1DUI, 1C13)~~. These data provide the three-dimensional coordinates (x, y, and z) for each atom in the solved structure, expressed in metric units, i.e. Angströms (10^{-10}m, Å). These data also contain the sequence and/or amino acid usage of the polypeptide. With this data, aligned as shown in FIGS. 16B and C, it was possible to calculate the three-dimensional distances between any desired atoms. Functional data regarding improved stability of the enzyme was taken from the literature (see below).

Please replace the paragraph at page 119, lines 4-16, with the following amended paragraph:

Optimal residues, to which the cross-link reaction is directed, were selected first based on the amino acid usage within the set of structurally and functionally related polypeptides, selecting for residues that in all of the polypeptides of the set are either Trp, Tyr, Phe, Lys, Pro, or His residues. From this set of residues, residue pairs were selected based on their average

alpha carbon distances within the set of structurally and functionally related polypeptides. Finally residue pairs were selected from the above set of residue pairs based on the proximity of the modeled tyrosine side-chains. This was done by modeling the mutations using the automated, knowledge-based protein modeling server Swiss Model, and visualizing the resultant polypeptides' structures, and with the program Swiss pdbViewer, both of which are available from the proteomics server of the Swiss Institute of Bioinformatics (SIB~~;~~ ~~www.expasy.ch~~). Additionally, residue pairs were selected that had previously been mutated to cysteines and formed disulfide bonds, stabilizing the enzyme and maintaining its activity.

Please replace the paragraph at page 124, lines 25-26, with the following amended paragraph:

National Brookhaven Laboratory Protein Database ~~(on-line at www.nbl.pdb.gov)~~

Please replace the paragraph at page 126, lines 6-7, with the following amended paragraph:

Pharmaceutical Research and Manufacturers of America. New Medicines in Develoment, Survey. ~~www.phrma.org/publications/industry/profile99/chap-2.html, 1998~~

Please replace the paragraph at page 127, lines 33-34, with the following amended paragraph:

Antibody Engineering Page, IMT, University of Marburg, ~~FRG:~~ FRG ~~http://aximt1.imt.uni-marburg.de/_rek/indexfenster.html~~